Highly Correlated Model-based Testing of Insulin Sensitivity

Initial results for a proposed low-intensity test

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Introduction

➤Type 2 Diabetes affects more than **230 million people** worldwide and is responsible for **3.5 million deaths** annually [1].
➤About **21 million Americans** are estimated to have type 2 Diabetes and an additional **54 million** are insulin resistant, prior to developing the disease [2].
➤Costs for the American health system: **$132 billion** in 2002, expected to rise over **$200 billion by 2020** [2].

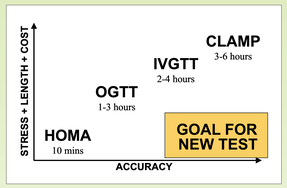
Early diagnosis of insulin resistance can reduce the burden of further complications and save lives and cost. Current diagnostic methods are too expensive and complicated to be useful in widespread population screening (euglycemic clamp, IVGTT), or not accurate enough to give more than a high/low result (HOMA, OGTT).
Currently insulin resistance rises ~7 years prior to diagnosis!

Test design

➤The proposed model-based test is designed to **measure same effects** as **gold-standard euglycemic-hyperinsulinemic clamp** and thus correlate highly.

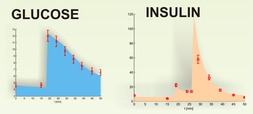
Design goals:
➤Simple, low intensity ➡ applicable in a clinical setting
➤High accuracy ➡ assess effects of intervention
➤Low cost ➡ population screening
➤Physiological dosing

The protocol:
1. Low dose **bolus of glucose** (10g) and **insulin** (1U)
➡ Reduce endogenous regulatory effects
➡ Improve clinical practicability and safety
2. Fit metabolic models to glucose, insulin and C-peptide
➡ Only transient data from 10 - 30 minutes post bolus
➡ Physiological model structure and parameter id
➡ Identification requires only few samples
3. Determine insulin sensitivity from model parameter S_I
➡ Inter-subject **variability only insulin dependent**, as in clamp



1. Inject glucose + insulin ➡ sample blood

2. Fit metabolic model to glucose and insulin samples

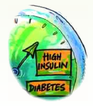


$$\dot{G} = -p_G G - S_I(G+G_E)\frac{Q}{1+\alpha_G Q} + \frac{P(t)}{V_G}$$

$$\dot{Q} = -n_C Q + \frac{n_I}{V_Q}(I-Q)$$

$$\dot{I} = -n_K I - \frac{n_I I}{1+\alpha_I I} - \frac{n_I}{V_P}(I-Q) + \frac{u_{ex}(t)}{V_P} + \frac{u_{en}(t)}{V_P}$$

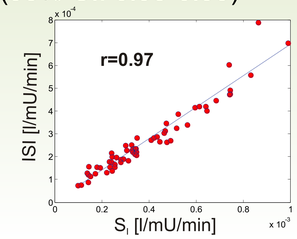
3. Get level of insulin resistance from model parameter S_I



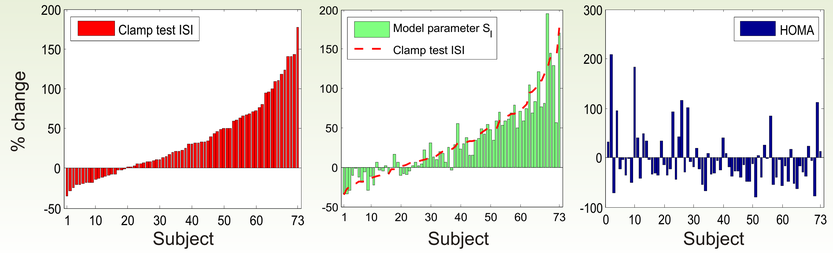
Performance analysis

1. <u>Model validation on euglycemic clamp data</u> [3]

Correlation clamp ***ISI*** vs. model ***S_I* in transient state: r=0.97**
(95% CI: 0.95-0.99)



Change in insulin sensitivity in intervention study by McAuley et al. [4]

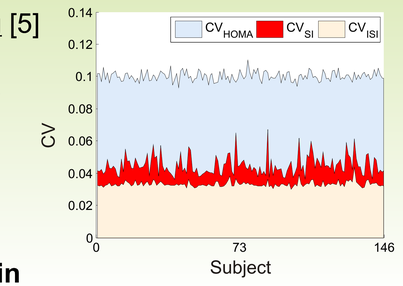


2. <u>Monte Carlo analysis of expected repeatability and effect of dosing</u> [5]

Test simulation on **virtual cohort** (**N=146**) generated from clamp trial data

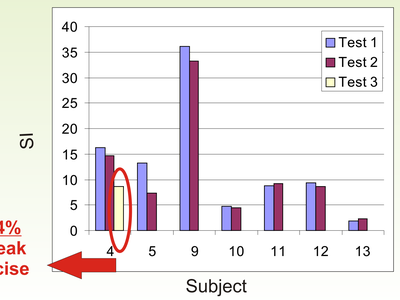
➤**Quantify effect of noise** and **unmodelled dynamics**
➡ **CV_{SI}=4.5%** (90% CI: 3.8% - 5.7%)

➤**Quantify effect of dosing**. (5g glucose / 0.5U insulin, 10g/1U, 20g/2U)
➡ Best noise/practicability compromise: **10g glucose / 1U insulin**



Clinical results

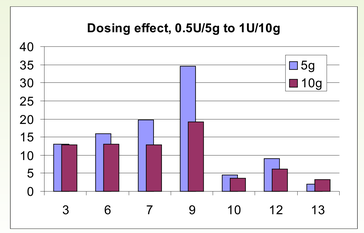
1. <u>Repeatability accuracy</u>
➤2 tests on same subject, 2-3 weeks apart
➤n=7 subjects, (n=3: 1U/10g, n=4: 0.5U/5g)
➡ **Mean error: 8.36%**

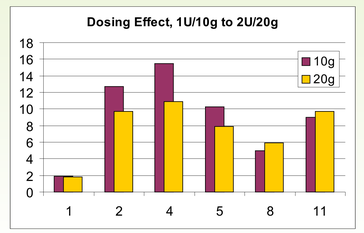


Reduction of 44% after 2 week break in regular exercise

2. <u>Effect of dosing(0.5U insulin/5g glucose, 1U/10g, 2U/20g)</u>

➤n=13 subjects (n=7: 0.5U/5g and 1U/10g; n=6: 1U/10g and 2U/20g)
➤Estimated S_I was typically higher for lower doses in each comparison.





[1] International Diabetes Federation (www.idf.org)
[2] American Diabetes Association (www.diabetes.org)
[3] Lotz T, Chase JG, et al. (2006), "Transient and steady state euglycemic clamp validation of a model for glycemic control & insulin sensitivity testing", DT&T 8(3)
[4] McAuley K, et al. (2002), "Intensive Lifestyle Changes Are Necessary to Improve Insulin Sensitivity", Diabetes Care 25(3)
[5] Lotz T, Chase JG, et al. "Monte Carlo analysis of a new model-based method for insulin sensitivity testing", Comput Meth Prog Bio, *in review*